Transition from potentiation to depression occurred over a narrow dose range, soleus being more susceptible to depression than FHL. High doses completely blocked twitches of both cat muscles stimulated indirectly. Directly stimulated curarized muscles were less depressed. There was also depression of twitches of the rat diaphragm at higher concentrations.

Doses of PMCG which potentiated twitch also potentiated low frequency tetani (5–30 Hz for soleus, 10–50 Hz for FHL), had little effect on intermediate frequency tetani (40–60 Hz and 80–100 Hz respectively), and depressed high frequency tetani (80 Hz and above and 150 Hz and above respectively). Tension at the higher frequencies was not maintained after PMCG. Doses sufficient to block twitch also reduced or abolished tetanic responses at all frequencies. Essentially similar results were obtained with the rat diaphragm.

It is concluded that, in low doses, PMCG potentiates contraction of skeletal muscle by an action mainly on the muscle membrane and not via the neuromuscular junction and that higher doses depress twitches (and tetani) by a similar action and probably partly by a curare-like action, similar to that of atropine (Bulbring, 1946).

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Observations on the neuromuscular blocking action of 2-(4-phenylpiperidino)-cyclohexanol (AH 5183)

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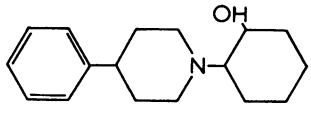
Oral administration of 2-(4-phenylpiperidino)-cyclohexanol (AH 5183), 10–20 mg/kg to mice, caused paralysis and death from respiratory arrest. As these effects resembled those seen after intravenous injection of neuromuscular blocking agents the effects induced by AH 5183 could have been mediated through similar mechanisms. This would be a novel property in a simple piperidine tertiary base.



AH 5183

In cats anaesthetized with chloralose maximal twitches of the tibialis anterior muscles were elicited by stimulation of sciatic nerves. In most experiments the contractions of both muscles were recorded simultaneously, one being excited once every second the other once every 10 sec. The neuromuscular block induced by AH 5183 varied with the frequency of stimulation; for example, AH 5183 (0·1 mg/kg intravenously) inhibited the twitches of the more rapidly stimulated muscle by 78%

without affecting the muscle contractions at the slow rate of stimulation. The duration of neuromuscular block was 50 min. At the time of maximum block the responses of the muscle to close intra-arterial injections of acetylcholine were decreased to a similar extent as the twitch response; a tetanus was poorly sustained and transiently antagonized the block. The response to direct stimulation of the muscle was unaffected. Neostigmine (0·1 mg/kg intravenously) only partially reversed the neuromuscular block induced by AH 5183 as also did choline. In conscious chicks AH 5183 (10 mg/kg intravenously) caused a flaccid paralysis which lasted 10–20 min. These results indicated that AH 5183 has a blocking action at the neuromuscular junction resembling that of (+)-tubocurarine. However, the high selectivity of action of AH 5183 on the tibialis anterior muscle stimulated at high rates indicated that the drug might also possess a prejunctional action in inhibiting either the uptake of choline or the synthesis of acetylcholine. The latter properties might be expected to be common to all cholinergic nerves. Accordingly, the effects of AH 5183 on the guinea-pig isolated ileum coaxially stimulated (Paton, 1957) were next investigated. At a concentration of 1 μg/ml. AH 5183 caused a 50–80% reduction in the responses to electrical stimulation without affecting the acetylcholine-induced responses of the preparation. The action of AH 5183 was very quick in onset and, after the drug was washed out of the bath, the responses of the preparation returned quickly to normal. These effects contrasted markedly with those of (+)-tubocurarine (10 μg/ml.), which had little or no effect on the responses of the ileum to acetylcholine or coaxial stimulation.

AH 5183 has a blocking action at the neuromuscular junction resembling that of (+)-tubocurarine, and also a pre-junctional inhibitory action on post-ganglionic parasympathetic nerves and perhaps at motor nerves. The nature of these actions is being further investigated.

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Effects of catecholamine beta-receptor blocking agents on striated muscle

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The depressant effects of propranolol on neuromuscular transmission and on the response of electrically stimulated muscle was thought to be due to the local anaesthetic action of the drug (Wislicki & Rosenblum, 1967). Two recently described compounds which in doses of a few micrograms block cardiac beta-adrenoceptors have a weak local anaesthetic effect or are apparently devoid of it: 4-(2-hydroxy-3-isopropylaminopropoxy)acetanilide (I.C.I. 50,172), in a concentration of 400 μg/ml., reduced the action potential only slightly (Dunlop & Shanks, 1968), and up to 6·4% of (±)-erythro-4-(2-methylamino-1-hydroxypropyl)methanesulphoanilide (MJ 1998) did not produce local anaesthesia (Lish, Weikel & Duncan, 1965).

In the sciatic nerve–gastrocnemius preparation of the frog (*Rana ridibunda* (L.)) I.C.I. 50,172 (900 μg/ml.) abolished the response to indirect and reduced the effect